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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO.
09/381,598	09/20/1999	MASAHIKO MIHARA	350292000800	4167

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	PAPER NUMBER
1646	10

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,598	MIHARA, MASAHIKO	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22, 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1 ☐ Certified copies of the priority documents have been received.

2 ☐ Certified copies of the priority documents have been received in Application No. _____ .

3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 24-32 were cancelled, claims 14-22 were amended, and new claims 33-38 were added in Paper No. 19, 12/9/2002. Claims 14-22, 33-38 are pending and under consideration.

Response to Amendment

The rejection of claims 24-32 under 35 USC § 102(b) has been obviated by cancellation of the claims, and is thus withdrawn.

The rejection of claims 24-32 under 35 USC § 103 has been obviated by cancellation of the claims, and is thus withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-22 stand rejected, and new claims 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gijbels et al (1995) in view of Vink et al. (1990), for reasons of record set forth in paper No. 17, 5/30/2002, and further in view of U.S. Patent No. 5,605,930 (Samid).

Gijbels et al. teaches the administration of antibodies to IL-6 in the EAE model of multiple sclerosis (page 799, Table I). The administration of the mAB to IL-6 significantly reduced the development of EAE, both in actively induced EAE and in the adoptive transfer

model of EAE. Gijbels does not disclose administration of antibodies to IL-6 receptor. Vink et al. teaches the administration of anti-IL-6 receptor antibodies (page 998, second column, third paragraph) as well as antibodies to IL-6 (page 998, Figure 1). These antibodies both block the action of IL-6 (page 998, column 2, third paragraph). Given the teaching of Gijbels of the beneficial effect of blocking the effect of IL-6 in the EAE model, along with the teaching of Vink that the effect of IL-6 can be neutralized by antibodies to both IL-6 and IL-6 receptor, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of administration of anti-IL-6 receptor antibodies to treat MS. The motivation is provided by Gijbels who concludes that the protective effect of anti-IL-6 in EAE might have therapeutic effect in inflammatory conditions of the CNS, including MS (page 804).

Applicant argues that there was no reasonable expectation of success for treating a sensitized T cell-mediated disease with an anti-IL-6 receptor antibody. Applicant argues that Gijbels fails to establish that the reported therapeutic effect was due to a reduction of IL-6 activity. However, Gijbels teaches that the protective effects of anti-IL-6 have been described in several in vivo models of autoimmune or inflammatory conditions, and that the conclusion from these studies is that antibodies to IL-6 are protective by neutralizing IL-6 activity (page 801, column 1, first full paragraph). The efficacy of the neutralizing effect of anti-IL-6 antibodies is shown in Figure 1(a) (Gijbels at 798). Applicant further argues that the administration of anti-IL-6 antibody increased IL-6 titer. However, the Gijbels reference teaches that this increase in IL-6 could not explain the protective effect in the EAE model because antibody to IL-6 must be present before day 8 (Figure 3, page 801 and page 801 column 2, first paragraph), and that IL-6 bioactivity is found in the sera and CSF of EAE induced animals.

Applicant further argues that there was no motivation to combine the Gijbels reference with the Vink reference. Applicant argues that the nature of the problem to be solved is not met by combining Gijbels with Vink. However, the Gijbels reference teaches a method of protecting against development of EAE by the administration of a protein with anti-IL-6 activity, in this case an anti-IL-6 antibody. The Gijbels reference further teaches that the protective effect of anti-IL-6 therapy in EAE would have therapeutic effects in MS (Gibels at 804, column 1). The Vink reference teaches the protective effects of both anti-IL-6 and anti-IL-6 receptor antibodies, both of which block IL-6 activity. As taught in the Gijbels reference, anti-IL-6 activity has protective benefits in the EAE model of MS.

Applicant further argues that there is no motivation to combine the Gijbels and Vink references because the cited prior art does not teach the combination. However, the Gijbels reference uses antibodies with anti-IL-6 activity in the art recognized MS mode, EAE, and further teaches that anti-IL-6 activity has protective benefits in the EAE model of MS (Gijbels at 804, column 1). The Vink reference teaches the efficacy of blocking IL-6 activity with either anti-IL-6 antibodies, or antibodies to IL-6 receptor.

Applicant further argues that there is no motivation to combine because one of ordinary skill in the art would not be motivated to practice the claimed method because of the complex nature of the in vivo activities of administered antibodies. However, the Vink reference shows that antibodies to IL-6 and IL-6 receptor have similar effects when administered, by blocking IL-6 activity, while the Gijbels reference teaches the efficacy of anti-IL-6 therapy in the EAE model of MS.

Claims 34-38 are drawn to methods of treatment as set forth in claim 14 wherein the disease is uveitis, thyroiditis, dermatitis and hypersensitivity. Gijbels and Vink do not teach the administration of antibodies directed to the IL-6 receptor for treatment of uveitis, thyroiditis, dermatitis and hypersensitivity. However, Samid discloses that IL-6, is a pleiotropic cytokine that plays a central role in defense mechanisms, including the immune-response, acute phase reaction and hematopoiesis. Samid further discloses that abnormal expression of the IL-6 gene has been suggested to be involved in the pathogenesis and/or symptoms of a variety of diseases, including non-malignant disorders associated with abnormal differentiation programs, autoimmunity and inflammatory processes, e.g., uveitis (column 66, lines 20-47). Given the disclosure of Samid of the central role that IL-6 plays in inflammatory processes, it would be an expected property of the method of administration of anti-IL-6 receptor antibodies to treat MS, that this method of administration would treat other autoimmune and inflammatory processes, such as uveitis, thyroiditis, dermatitis and hypersensitivity.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 3, 2003